

REMARKS

The Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

I. Status of the Claims

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

Claims 2, 16, 19-23 and 40-93 are requested to be canceled, without prejudice or disclaimer.

Claims 1, 13, 24-26 and 28 are currently being amended. Claim 1 is amended to delete the recitation of "about." Claim 13 is amended to delete the recitation of the trademark symbol. Claims 24, 25, 26, and 28 are amended to state that the composition of claim 1 is formulated into a solid dosage form, and that the redispersed particle sizes of the claims refers to the solid dosage form redispersed particles. *See e.g.*, the application at paragraphs [0064] – [0073], [0148], and [0035].

It is acknowledged that the foregoing amendments are submitted after final rejection of the claims. However, because the foregoing amendments do not introduce new matter, and either place the application in condition for allowance or at least in better condition for appeal. Thus, entry thereof by the Examiner is respectfully requested.

After amending the claims as set forth above, claims 1, 3-15, 17-18, 24-39 are now pending in this application.

II. Claim rejections – 35 U.S.C. § 112

Claims 24-28 were rejected as allegedly lacking antecedent basis for the claim term “particle size of less than 2 microns and less than 1900 nm.” The Applicant respectfully disagrees with this ground for rejection.

Claim 1 is directed to a nifedipine composition comprising nifedipine crystalline particles having an effective average particle size of less than about 1000 nm. Claims 24-25 define the *redispersed* particle size of the composition of claim 1 *following administration to a mammal*. To clarify this distinction, claim 24 has been amended to state that the composition of claim 1 is formulated into a solid dosage form; claim 24 refers to the redisersed nifedipine particle size of a solid dosage form of the nifedipine composition of claim 1. Redisersed drug particle sizes may be larger than the original formulation drug particle sizes due to agglomeration when exposed to various pH conditions present in the mammalian body.

Similarly, claims 26-28 define the *redispersed* particle size of the composition of claim 1 *following redispersion in a biorelevant media*. To clarify this distinction, claim 26 has been amended to state that the composition of claim 1 is formulated into a solid dosage form, and that the redisersed particle sizes refer to the redisersed solid dosage form particles.

As the amended claims are definite, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112 is respectfully requested.

III. Claim rejection – 35 U.S.C. § 103

The Office Action presents three different § 103 rejections; however, none of the three establish a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness:

...three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

M.P.E.P. § 2143.

Moreover, it should be noted that, “the proposed modification cannot render the prior art unsatisfactory for its intended purpose.” (MPEP § 2143.V). Finally, if an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious.” (MPEP § 2143.03).

Here, none of the cited reference, alone or in combination, teach or suggest all the claim limitations. Nor do the references teach or motive one of skill in the art to modify the reference, especially in light of the knowledge generally available in the art. Moreover, in some instances, the proposed modification may render the prior art unsatisfactory for its intended purpose.

A. U.S. Patent No. 5,145,683

Claims 1, 3-15 and 24-39 were rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over U.S. Patent No. 5,145,683 to Rhodes (“the ‘683 Patent”). According to the rejection, the ‘683 Patent describes nifedipine crystals having a particle size of less than 100 microns and using polyvinyl pyrrolidone as a surface stabilizer. (Office Action at 3-4). The Office Action asserts that it would have been obvious to choose an appropriate particle size of nifedipine because the ‘683 Patent suggests that both a quick release formulation and a slow release formulation are attained with a particle size of less than 100 microns. (Office Action at 4). The Applicant respectfully traverses the rejection.

Claims 1, 3-15 and 24-39 are not obvious in light of the cited reference because there is no teaching, suggestion or motivation to modify the reference, and the reference does not teach or suggest all the limitations of claims. As such, a *prima facie* case of obviousness has not been established.

First, there is no teaching or suggestion to modify the size of the nifedipine particles to **less than 1000 nm** (*i.e.* 1 micron), as recited in the claims of the present application. The Applicant teaches and claims a nanoparticulate composition having “an effective average particle size of less than about 1000 nm.” This is defined in the application as a composition in which “at least 50% of the particles have an average particle size of less than about 1000 nm.” See paragraph [0130] of the application.

As asserted by the Office Action, the ‘683 Patent relates to “a slow release formulation containing nifedipine.” (Office Action at 2). As recited in the ‘683 patent, such a formulation has a “particle size of 100 micrometers or less...” and “preferably...a particle size of less than 25 micrometers, more preferably a particle size in the range of from 10 to 25 micrometers.” (‘683 col. 2, lines 9-10 and lines 35-27). Thus, the preferred range of particle size for the slow release formulation of the ‘683 Patent is less than 100 microns, less than 25 microns, and **more preferably from 10 to 25 microns**; however, there is no teaching or suggestion to make or use particles of less than 10 to 25 microns.

In fact, because a “more preferable” particle size is recited to include particles in the 10 to 25 micron range, this reference *teaches away* from the use of particle smaller than 10 microns. Thus, to develop a slow release formulation as per the teaching of the ‘683 Patent, one skilled in the art would focus efforts on nifedipine particles of a much larger size (*e.g.*, **larger by at least 10-fold**) than those of the claimed invention. The ‘683 Patent does not motivate one to attempt such formulations with particles of **less than 1 micron**, nor does the knowledge generally available in the art provide a reason to do so.

As described in more detail below, it is well known in the art that smaller particles generally have the effect of enhancing or increasing drug absorption and thus speeding onset; as noted in the specification, “the dissolution and resultant absorption of the nifedipine will correspond to the particle size of the drug.” (See present Application, US 2004/0115134 at paragraph [0024]). Accordingly, the knowledge available to one skilled in the art would not motivate one to modify the particles of the ‘683 Patent because, as noted in the Office Action, the ‘683 Patent teaches a **slow release formulation**. (Office Action at 2). Moreover, modification of the prior art to smaller particles would likely render the claimed invention

unsatisfactory for its intended purpose; that is, particles of **less than 1 micron** may render the formulations of the '683 Patent inadequate or less desirable as slow release formulations.

Second, the '683 Patent does not teach or suggest all the elements of the claims. As noted above, there is no suggestion or teaching to make nifedipine particles smaller than 10 microns, and although the '683 Patent discloses a genus of nifedipine particles (*e.g.*, particles with a size of less than 100 microns, or less than 25 microns), “[t]he fact that a claimed species or subgenus is encompassed by a prior art genus is **not sufficient by itself to establish a *prima facie* case of obviousness.**” MPEP § 2144.08 II. Moreover, “it is **essential** that [there be] some motivation or suggestion to make the claimed invention in light of the prior art teachings.” (*Id.* at A). Because the '683 Patent teaches a genus of less than 100 microns, and a genus of less than 25 microns **but also places a lower limit of 10 microns** as being even more preferred (*i.e.*, a range of particle size between 10 - 25 microns), there is clearly no suggestion or teaching, either expressly or inherently, to make and use particles of a smaller size. Conversely, **there is an express teaching to make and use much particles of a much larger size**, *i.e.* particles of 10 to 25 microns.

Accordingly, for at least the reasons stated above, the artisan of ordinary skill would not have found the present invention obvious based on the teaching of the '683 Patent. As such, the Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. § 103 over the '683 Patent.

B. U.S. Patent Nos. 4,562,069 and 5,145,683

Claims 1, 3-15 and 24-39 were rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over U.S. Patent No. 4,562,069 (“the '069 Patent”) alone or in view of U.S. Patent No. 5,145,683 (“the '683 Patent”). According to the rejection, the '069 Patent relates to nifedipine compositions wherein the nifedipine has a particles size of about 1 to 10 microns, but fails to teach particles **less than 1000 nm**. (Office Action at 3). The Office Action continues “it would have been obvious to one of ordinary skill in the art...to choose an appropriate particle size of the microcrystalline nifedipine in the composition of the '069 because the difference between the claimed upper limit of particle size and the lower limit

taught by ‘069 is 1 nm.’’ (Office Action at 3-4). The Applicant respectfully traverses this rejection. Similar to the ‘683 Patent discussed above, the ‘069 Patent alone does not establish a *prima facia* case of obviousness; there is no teaching, suggestion or motivation to modify the reference, and the reference does not teach or suggest all the limitations of claims.

As described for the ‘683 Patent, the ‘069 Patent also lacks any suggestion or motivation to modify the nifedipine particle size to **less than 1000 nm**, even in light of the knowledge available to one of skill in the art at the time of filing. Moreover, the ‘069 Patent lacks any teaching of nifedipine particles **having an effective average particles size of less than 1000 nm**. In fact, nowhere does the ‘069 Patent mention, teach or suggest making or using particles smaller than 1000 nm or that particles of such a size would be advantageous.

The Office Action asserts that because the range of particle size preferred in the ‘069 Patent is between 1 and 10 microns, a particle size of less than 1 micron would be obvious to one skilled in the art. This assertion is unfounded. First, the ‘069 Patent states “[n]ifedipine crystals which have a mean particle diameter of about 10 to 1 micron...are preferably employed as the proportion of crystalline nifedipine.” (‘069 at col. 2 lines 27-30). Similar to the size range taught in the ‘683 Patent, the lower limit particle size of 1 micron cannot be construed to encompass, teach, or suggest particles with an average effective particle size of **less than 1 micron** (*i.e.*, at least 50% of the particles having an average effective particle size of less than about 1000 nm).

Second, because the ‘069 Patent teaches the use of crystalline nifedipine for delayed onset and longer duration of action in a two-phase medicament, (see e.g., ‘069 Specification at col. 1 lines 50-61 and col. 2 lines 8-12) it would not be obvious to one of skill in the art to use smaller particles for a such a formulation. Crystal size plays a role in onset and duration of drug effect. It was well known to those skilled in the art at the time of filing that “as the particle size of a drug decreases, its surface area increases, and therefore, its absorption into the body becomes quicker.” (See e.g., U.S. Patent No. 4,540,602, raised in the previous Office Action, *e.g.*, at col. 4, lines 44-46). Indeed, the ‘069 Patent confirms the importance of crystal size in drug effect onset and duration, noting that “attempts have been made, by **selecting a particular crystal size**, to increase the absorbability and bioavailability on oral

administration” and that “[t]he resulting tablets have a markedly longer action” and that “the onset of action is considerably delayed.” (*See e.g.*, ‘069 col. 1, lines 55-59). Thus, the teachings of the ‘069 Patent would lead one skilled in the art to focus efforts on nifedipine particles of a particular size—**namely, those between 1 and 10 microns**—to derive successful slow release formulations with delayed onset. One skilled in the art would not be motivated by the teaching of the ‘069 Patent to make or use nifedipine particles with an average effective size of **less than 1000 nm**. Moreover, it is likely that a smaller average effective particle size would render the ‘069 formulation unsatisfactory for its intended purpose. That is, the delayed onset and extended duration of the crystalline formulations (*e.g.*, an 8 to 24 hour period, as per the specification of the ‘069 Patent at col. 3, lines 33-34 and tables 1 and 2) may not be expected to be maintained with a smaller particle size.

Because there is no teaching, expressly, explicitly or implicitly, to make or use smaller crystalline molecules, and because such a modification would likely render the ‘069 invention unsatisfactory for its intended purpose, one skilled in the art would not find the compositions of the present application obvious in light of the teaching of the ‘069 Patent.

The Office Action also asserts that the teachings of the ‘069 Patent in conjunction with the teachings of the ‘683 Patent render claims 1, 3-15 and 24-39 obvious. However, as previously stated, neither reference, alone or in combination, teaches or suggests every element of the claimed invention (crystalline nifedipine particles having an average effective particle size of less than 1 micron). Further, there is no motivation in the references themselves or in the knowledge generally available to one skilled in the art to modify the references. Accordingly, the Applicant respectfully requests that the rejection under 35 U.S.C. § 103 over the ‘069 Patent alone or in combination with the ‘683 Patent be withdrawn.

C. U.S. Patent Nos. 4,562,069 and 5,145,683 and 4,814,175

Claims 17-18 were rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over U.S. Patent No. 4,562,069 (“the ‘069 Patent”) alone or in view of U.S. Patent No. 5,145,683 (“the ‘683 Patent”) and further in view of U.S. Patent No. 4,814,175 (“the ‘175 Patent”). According to the rejection, the ‘069 and the ‘683 Patents “fail to teach the claimed combination of nifedipine with other agents.” (Office Action at 4). The Office Action continues that because the ‘175 Patent teaches “a combination of particulate nifedipine and a beta blocker” it would have been obvious for one of ordinary skill at the art to combine these teachings to derive the subject matter of claims 17 and 18. (Office Action at 4-5). The Applicant respectfully traverses the rejection.

The ‘175 Patent is similarly deficient to the ‘069 Patent and the ‘683 Patent in that it does not teach or suggest nifedipine particles having a size of less than 1 micron, nor does it motivate the skilled artisan to modify nifedipine particles to this size range.

The ‘175 Patent teaches nifedipine particle diameters of 10-50 microns and relates to delayed release nifedipine compositions (‘175 abstract; col. 1 lines 43-44). Similar to the ‘683 and the ‘069 Patents discussed above, to obtain the desired delayed release (*e.g.*, 24 hour effectiveness, ‘175 at col. 2, lines 3-7), larger diameter particles of nifedipine are used, specifically **particles between 10-50 microns and more preferably 15-50 microns** in diameter. (‘175 at col. 1 lines 43-44). This particle size is **at least 10-fold greater** than the particle size taught and claimed by the Applicant. Similar to the particle size range of the ‘683 Patent and the ‘069 Patent, a particle size range of 10-50 microns or 15-50 microns does not include and cannot be construed to encompass or suggest nifedipine particles with an average effective particle size of less than 1000 nm. Further, there is an explicit teaching to use particles of the 15-50 micron range; similar to the ‘683 Patent, this **teaches away** from attempting such formulations with a smaller particle size. Finally, a smaller particle size may render the prior art unsatisfactory for its intended purpose; that is, the effects of delayed release and extended duration (*e.g.*, 24-hour effectiveness) may not be maintained.

Thus, the skilled artisan at the time of filing, when presented with all three references alone or in combination would not find the subject matter of the present application obvious. None of the reference teach, describe or suggest making or using nifedipine particles with an average effective particle size of less than 1 micron. Further, reducing the particle size of the '683, the '069 or the '175 invention could render these compositions unsatisfactory for their intended purpose. As such, the rejection under 35 U.S.C. § 103 over the '069 Patent alone or in view of the '683 Patent and further in view of the '175 Patent should be withdrawn.

IV. Conclusion

The Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

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If any extensions of time are needed for timely acceptance of papers submitted herewith, the Applicant hereby petitions for such extension under 37 C.F.R. § 1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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